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Chapter 7

Targeted Therapies in Platinum-Resistant Ovarian Cancer: Advances in Immunotherapy Combination Strategies

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Additional information is available at the end of the chapter

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Abstract

Platinum-resistant ovarian cancer (OC) is one of the most lethal gynecological malignancies that has shown minimal improvement in 5 year overall survival rates for the past 15 years. This chapter discusses the current targeted therapies that are being used or evaluated as monotherapy and/or adjuvants to chemotherapeutic regimens in platinum-resistant ovarian cancer. These therapeutics include focal adhesion kinase inhibitors (FAK) such as defactinib, anti-angiogenic agents such as bevacizumab, poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitors such as olaparib, epidermal growth factor receptor family targeting agents such as erlotinib, folate receptor antagonists such as farletuzumab, and insulin growth factor receptor inhibitors such as linsitinib. The rationale for using immunotherapeutic agents will also be discussed. The importance of combination strategies utilizing immunotherapies will be highlighted with specific focus on immune checkpoint inhibitors that are currently in multiple clinical trials assessing synergistic effects with targeted agents such as PARP inhibitors in platinum-resistant OC. These therapeutic combinations have the potential to produce substantial improvements in platinum-resistant OC treatment outcomes in the future. Finally, the major challenges and limitation associated with these combination therapies and strategies to overcome them will be explored.

Keywords: ovarian cancer, platinum resistance, targeted therapy, immunotherapy, combination strategies

1. Introduction

Ovarian cancer (OC) is the leading cause of death from gynecologic malignancies in the United States [1]. It is estimated that 22,240 women will be diagnosed with OC, and 14,080

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women will die of the disease in 2017 [1]. Ovarian malignancies can be primary (arising from normal structures within the ovary) or secondary (arising from non-ovarian tissue). Approximately 90% of all primary OC are epithelial carcinomas [2]. Epithelial ovarian cancer (EOC) is sensitive to many chemotherapeutic agents, and the current standard treatment consists of cytoreductive surgery followed by chemotherapy with platinum compounds such as cisplatin or carboplatin and a taxane agent such as paclitaxel [3]. A high percentage of patients with advanced EOC however, eventually develop recurrent disease within 3 years and only 10–30% of patients presenting with stage III or IV disease survive 5 years following initial diagnosis [3, 4]. This poor survival rate is mainly due to the development of chemotherapy resistance following several rounds of treatment. In many cases, initial recurrences are platinum-sensitive but the disease eventually becomes platinum-resistant; which is defined as disease progressing within 6 months of platinum-based therapy [4, 5]. Platinum-resistant patients are subsequently limited to non-platinum and non-taxane chemotherapy treatment options such as topotecan, gemcitabine, and pegylated liposomal doxorubicin which have shown moderate therapeutic success [6]. Alternative treatment options for platinum-resistant disease are, therefore, constantly being explored and immunotherapy and targeted agents are increasingly undergoing clinical trials which are showing positive results.

2. Platinum compounds and mechanisms of resistance

The serendipitous discovery that platinum coordination complexes blocked bacterial replication led to the hypothesis that these complexes could be of great clinical value as anti-tumor agents [7]. Cis-diamminedichloroplatinum II (cisplatin) was the first drug in its class successfully marketed followed by carboplatin and oxaliplatin. All three drugs have similar mechanisms of action. Cisplatin and carboplatin are approved for the treatment of OC; while tumor cell resistance mechanisms to both drugs are similar they differ in their pharmacokinetic and toxicity profiles [8]. Oxaliplatin is highly effective in colorectal cancers because it's mechanism of action (MOA) is not limited to that of the other platinum compounds [8].

Cisplatin, the prototype platinum compound, is taken up into cells by passive diffusion or via the active copper transporter 1 (CTR1) [9]. The subsequent activation of cisplatin is mediated by the displacement of chloride atoms by water to form a highly reactive electrophile that targets nucleophilic sites on DNA and DNA-associated proteins. The N-7 guanine base is most susceptible, although the O-6 guanine, N1, N3 adenine, and N3 cytosine are also targeted. Cisplatin DNA interactions result in the formation of both mono- and bifunctional adducts with the latter forming cis-Pt (NH3)2-d(GpG) at twice the rate of cis-Pt (NH3)2-d(ApG). Interstrand crosslinks are not as common. The bulky adducts between DNA and cisplatin can bend the helix and unwind DNA. The critical importance is the recognition of DNA-cisplatin adducts by proteins that either initiate DNA repair by nucleotide excision repair (NER) or inhibit repair through high mobility group (HMG) proteins. Platinum compounds are cell cycle non-specific (CCNS) causing arrest in S/G2 [9].

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Multiple mechanisms are thought to play a role in tumor cell resistance to cisplatin due to the heterogeneity of the disease. Resistance to cisplatin typically confers resistance to carboplatin, but not to oxaliplatin. Some common mechanisms of tumor cell resistance to cisplatin in OC includes increased repair to damaged DNA [10], drug efflux by copper efflux transporters ATP7A [11] and ATP7B [12], reduced uptake by CTR1 [13], and increased expression of glutathione and GSH-S-transferase, which are electron donors forming conjugates with cisplatin and rendering it inactive [10]. Both increased efflux and reduced uptake result in reduced drug accumulation. Overexpression of epidermal growth factor (EGF) and its receptor (EGFR) in cancer cells are critical for growth and survival and EGFR overactivity using autocrine and/or paracrine signals is associated with platinum resistance [14]. The overexpression of the tyrosine kinase; focal adhesion kinase, has also been linked to platinum resistance in OC through several mechanisms including increased expression of the transcription factor OCT4 and the cell surface protein N-cadherin, as well as increased aldehyde dehydrogenase (ALDH) activity [15, 16].

3. Targeted therapies in platinum-resistant ovarian cancer

Although there are many chemotherapeutic agents available, the level of response of platinum-resistant ovarian cancer (OC-Pt) to these drugs is increasingly diminished as the disease progresses [17]. In the past decade, this has fueled a consistent increase in the development of targeted therapies aimed at either supplementing chemotherapeutic regimens or providing novel monotherapy in OC-Pt [17]. Categories of targeted drugs that are undergoing clinical trials or have received FDA approval for OC-Pt include focal adhesion kinase (FAK) inhibitors, poly(adenosine diphosphate [ADP] ribose) polymerase (PARP) inhibitors, anti-angiogenic agents, epidermal growth factor receptor targeting agents, folate receptor antagonists, and insulin growth factor receptor inhibitors.

3.1. PARP inhibitors

PARP inhibitors are a group of targeted drugs that have been at the forefront of emerging OC-Pt therapeutics over the past decade [18, 19]. Human PARPs comprise a total of 17 enzymes [20]. The PARP-1 isoform was the first member of the family to be described and it is the major active PARP enzyme in human cells with the remainder of activity mainly attributed to the PARP-2 isoform [21]. Both PARP-1 and PARP-2 are DNA damage repair enzymes [21]. Human PARP-1 (113 kDa) is a nuclear protein/enzyme which binds with DNA and promotes DNA repair by releasing PARP-1 from DNA and allows recruitment of proteins involved in both base excisional repair (BER) and homologous recombination [22]. Human PARP-2 (62 kDa) is a nuclear protein that binds less efficiently to DNA single-strand breaks but instead recognizes gaps and flap structures [23]. These DNA repair properties of PARPs have made them important anticancer targets in a variety of cancers including OC.

The inhibition of PARP enzymes, especially PARP-1, results in an excess of single-strand breaks, which subsequently causes double-strand breaks to occur as DNA replicates [24]. Under normal circumstances, defects such as double-strand breaks are usually repaired by the homologous recombination process that involves breast cancer type susceptibility (BRCA) proteins. Tumors with defective homologous recombination, including BRCA1/2-mutated OCs, are therefore very sensitive to PARP inhibition [25].

PARP inhibitor drugs are able to cause cancer cell death by inhibiting repair of single-strand breaks and subsequently trapping PARP on DNA, forming cytotoxic PARP-DNA complexes [25]. Several small molecular PARP inhibitor drugs are now undergoing clinical trials and two of them (olaparib and rucaparib) have already been approved by the FDA for use in OC-Pt.

Olaparib (Lynparza), a product of AstraZeneca, received approval from the U.S. Food and Drug Administration (FDA) in December 2014. Olaparib is an inhibitor of several PARP enzymes, including PARP1, PARP2, and PARP3 [26]. The orally administered drug is used for monotherapy in patients with germline BRCA-mutated advanced recurrent OC-Pt [26]. Phase II clinical trials have shown that olaparib significantly improves progression-free survival (PFS) in OC-Pt with similar rates of response reported in patients with BRCA1- and BRCA2-mutated disease [26]. The most common side effects observed with olaparib were mild gastrointestinal irritation, anemia, and severe fatigue.

Rucaparib (Rubraca), a product of Clovis Oncology, was granted accelerated approval from the FDA on December 19, 2016 for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated with advanced OC, which had been treated with two or more chemotherapies that included those with OC-Pt. Rucaparib is also a non-specific inhibitor of several PARP enzymes, including PARP1, PARP2, and PARP3 [27]. The ARIEL2 and Study 10 clinical trials produced critical integrated efficacy and safety data in OC-Pt patients which showed that the average response rate was approximately 25% with minimal differences between patients who harbored a BRCA1 mutation, and those who harbored a BRCA2 mutation [27]. Adverse reactions to the drug included fatigue, anemia, dysgeusia, and decreased appetite [27].

A third PARP inhibitor niraparib (Zejula), a product of Tesaro, was approved on March 27, 2017 to maintain treatment of adult patients with recurrent epithelial ovarian and fallopian tube cancer that is completely or partially responsive to platinum-based chemotherapy. Niraparib inhibits both PARP1 and PARP2 and currently has no specific indications in OC-Pt [28].

It is generally accepted that the major categories of cancers that are sensitive to PARP inhibitors are BRCA-mutated cancers. Interestingly, drug resistance to PARP inhibitors have been linked to the development of secondary mutations in the BRCA gene themselves [29]. These secondary mutations can restore functional BRCA1 or BRCA2 genes leading to deleterious consequences in patients with cancer [29]. Other mechanisms of resistance to PARP inhibitors include increased multi drug resistance protein-1 (MDR-1) activity, which leads to increased

drug efflux from cancer cells as well as reduced expression of tumor suppressor p53-binding protein 1 (TP53BP1), which is required for non-homologous end-joining DNA repair [30]. Many of these resistance mechanisms are active in OC-Pt [10–16] and therefore can potentially circumvent the therapeutic effects of PARP inhibitors. Nonetheless, PARP inhibitors show much promise in OC-Pt therapeutics.

3.2. Anti-angiogenic therapies

Solid tumors rely on neovascularization for growth and survival in hypoxic environments. The process of angiogenesis is critical for normal ovarian function and for growth, development, and metastasis of OC cells [31]. The hypoxic environment drives angiogenesis in solid tumors which requires continual and persistent growth of new blood vessels [32]. Data strongly suggest a close correlation between increased levels of hypoxia-inducible factor 1-α (HIF 1-α); a transcription factor stabilized during hypoxia and vascular endothelial growth factor (VEGF) in EOC [33]. VEGF is a potent pro-angiogenic growth factor that is upregulated during hypoxia and is elevated in epithelial ovarian neoplasms [33]. VEGF-A is a major pro-angiogenic growth factor that binds to VEGF receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2), although VEGFR2 is considered the major target. The VEGF-A/VEGFR-2 interaction activates the RAF/MAPK and PI3K/AKT signaling pathways favoring both proliferation and survival of endothelial cells. Intratumoral protein levels of VEGFR-2 were found to be significantly higher in platinum-resistant OC compared to platinum-sensitive OC patient tumors [34]. Many agents targeting angiogenesis have been developed and several have shown some degree of clinical efficacy in OC-Pt. The anti-angiogenic group of drugs include bevacizumab, aflibercept, nintedanib, trebananib, pazopanib, sunitinib, sorafenib, and cediranib.

Bevacizumab (Avastin), a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF)-receptor ligand VEGF-A, is the most extensively investigated anti-angiogenic agent in clinical OC research. Currently, it is the only anti-angiogenic drug that is FDA approved for the treatment of OC as monotherapy or in combination regimens with paclitaxel, topotecan, doxorubicin (pegylated), carboplatin, or gemcitabine for recurrent OC-Pt [35]. Bevacizumab potentiates the cytotoxic effect of chemotherapeutic agents by reducing interstitial fluid pressure and vascular permeability to increase delivery of cytotoxic drugs to cancer cells [35].

A phase II trial of bevacizumab as a single agent in OC-Pt reported that 40.3% of these patients survived progression free for at least 6 months while median PFS and overall survival were 4.7 and 17 months, respectively [36]. Common adverse effects related to bevacizumab were hematologic and gastrointestinal [36].

Subsequent randomized phase III clinical trials focused on the use of bevacizumab with standard chemotherapeutic regimens as first-line treatment in both platinum-sensitive and platinum-resistant OC. AURELIA was the first randomized phase III trial (Study ID#: NCT00976911) to evaluate combined bevacizumab with chemotherapy in OC-Pt [37]. All

patients received standard chemotherapy with either paclitaxel or topotecan or liposomal doxorubicin. Patients randomized to arm 2 of the study received bevacizumab (10 mg/kg IV every 2 weeks or 15 mg/kg IV every 3 weeks) concomitantly. The study showed improved PFS and overall response rate with no new safety concerns. The percentage of adverse events associated with chemotherapy + bevacizumab was 57.0% versus 40.3% (chemotherapy alone). Proteinuria and hypertension had the highest incidence rate, whereas gastrointestinal perforations were comparable 2% (bevacizumab) versus 0% (bevacizumab + chemotherapy). Treatment arms that consisted of a higher exposure to chemotherapy in the bevacizumab + chemotherapy combined study group, had a higher incidence rate of hand-foot syndrome and peripheral sensory neuropathy.

The topoisomerase I inhibitor Irinotecan (Camptosar), in combination with bevacizumab was evaluated in recurrent OC in an open-label randomized phase III trial (Study ID#: NCT01091259) [38]. This cohort included 19 patients with OC-Pt. The objective response rate for all patients entered was 27.6% and the clinical benefit rate was 72.4%. Adverse events with the addition of bevacizumab relative to GI toxicity was limited to <3% and considered acceptable [38]. These studies show that it is clinically proven that bevacizumab + chemotherapy demonstrate efficacy in OC-Pt and that safety can be achieved with the right dose and combination of drugs.

Pazopanib (Votrient) is an oral anti-angiogenic multi-targeted tyrosine kinase inhibitor with activity against VEGFR-1, 2, and 3. Pazopanib is currently FDA approved for advanced renal cell carcinoma and soft tissue carcinoma. The PACOVAR study (Study ID#: NCT01238770) evaluated pazopanib in combination with metronomic cyclophosphamide in 16 patients with platinum-resistant EOC [39]. Metronomic chemotherapy is the close, regular administration of chemotherapy drugs at low, minimally toxic doses, with no prolonged break periods. In the PACOVAR study, median PFS and overall survival were 8.35 and 24.95 months, respectively. The most common adverse events were elevation of liver enzymes, leukopenia, diarrhea, and fatigue. Altogether, five serious adverse events developed in four patients. The study concluded that pazopanib + metronomic cyclophosphamide was a feasible regimen for patients with recurrent OC-Pt.

Pazopanib has also shown promising results in mice injected with a highly aggressive cisplatin-resistant SKOV-3 clone of OC cells in combination with metronomic oral topotecan (toperisomerase I inhibitor) [40].

Aflibercept (Ziv-aflibercept/VEGF-trap) mimics the VEGF receptor and has similar ligand binding components to VEGFR-1 and VEGFR-2 [41]. Aflibercept binds to circulating VEGFs and acts like a "VEGF trap" [42]. This primarily results in suppression of VEGF-A and VEGF-B activity and subsequently inhibits the growth of new blood vessels in tumors [42]. Aflibercept was administered at two doses in a randomized, double-blind, phase II trial that assessed response evaluation criteria in solid tumor response rates, as a single agent treatment in recurrent OC-Pt (Study ID#: NCT00327171). The study concluded that the treatment was well tolerated by the patients but the required objective response rate endpoint was not achieved [43]. The participants in this study had received 3–4 prior chemotherapy

lines and were resistant to liposomal doxorubicin or topotecan. Hypertension was the most common toxicity observed.

3.3. Focal adhesion kinase (FAK) inhibitors

Focal adhesion kinase (FAK) is a non-receptor cytoplasmic tyrosine kinase that is encoded by the protein tyrosine kinase 2 (PTK2) gene, and is found in most tissues in the human body [44]. PTK2 gene amplification with subsequent increased activation through phosphorylation occurs in many OCs, where it is involved in promoting cancer cell migration, invasion, adhesion, proliferation, and survival [45–47]. High FAK activity is generally associated with worse overall cancer patient survival [48, 49]. Several studies have shown that FAK expression is significantly increased in OC-Pt, and that this platinum resistance is associated with increased tumor-associated aldehyde dehydrogenase (ALDH) activity, as well as overexpression of X-linked inhibitor of apoptosis (XIAP) [16, 50]. We have also demonstrated in our studies that platinum-resistant OC cells are resensitized to cisplatin when co-treated with a FAK inhibitor [15].

Several FAK inhibitors have been developed to prevent FAK activation by blocking its phosphorylation sites; which halts its downstream signaling pathways with subsequent reduction in ovarian tumorigenesis and cancer progression. A few of these drugs are now in clinical trials. The FAK inhibitor defactinib from Verastem was evaluated in a phase I study (Study ID#: NCT00787033) which found that OC-Pt patients achieved a prolonged PFS [51]. Defactinib produced grade 1–2 adverse events that were easily managed and reversible, even with continued dosing [51]. A phase I/Ib, open-label (Study ID#: NCT01778803) multicenter, dose-escalation trial of paclitaxel in combination with defactinib was subsequently initiated in OC-Pt patients with advanced cancers [52]. The combination was found to be efficacious with no apparent increase in the severity and incidence of paclitaxel-related toxicities.

A phase I/Ib, open-label, multi-center, dose-escalation, and dose expansion trial (Study ID#: NCT02943317) to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of defactinib in combination with the human monoclonal PD-L1 antibody avelumab in recurrent or refractory stage III–IV OC is currently ongoing, and is expected to enroll approximately 100 patients at up to 15 sites across the United States. The FAK inhibitor GSK2256098 was also evaluated in a phase I clinical trial (Study ID#: NCT01138033) in patients with advanced solid tumors including OC-Pt [53]. GSK2256098 significantly reduced FAK activity in tumors of patients that received the drug at a dose of 750 mg twice daily.

FAK inhibition is still an emerging area in OC-Pt therapeutics and many clinical trials are underway that will provide more insight into their efficacy in different histological types of OC.

3.4. Folate receptor antagonists

Folate receptors (FRs) are proteins that bind folate with high affinity. The FR-α and FR-β isoforms are well characterized as membrane-bound receptors that facilitate the binding

and subsequent internalization of folate compounds and their chemical derivatives [54]. The FR-α receptor is significantly overexpressed in EOC where it promotes tumor growth by either an aberrant folate uptake mechanism or dysregulated signaling pathways [55]. The FR-α receptor can also induce platinum resistance by regulating the expression of apoptosis-related molecules; Bcl-2 and Bax and a higher expression of FR-α level has been linked to poor prognosis in OC patients [56]. These properties of the FR-α receptor makes it a prime therapeutic target for OC. In recent years, two drugs (vintafolide and farletuzumab) have gained relevance as FR-α receptor antagonist applicable in OC-Pt. Farletuzumab (MORAb-003), a monoclonal antibody to FR-α was evaluated in a phase III trial (Study ID#: NCT00738699) in combination with paclitaxel for advanced OC-Pt patients [57]. The drug was developed by Morphotek and the study was unfortunately discontinued because of minimal changes in PFS and the occurrence of serious adverse events including neutropenia and atrial fibrillation [57].

Vintafolide (originally known as EC145), is a water-soluble derivative of folic acid that is conjugated to the vinca alkaloid 'desacetylvinblastine hydrazide' [58]. The combination of vintafolide with pegylated liposomal doxorubicin (PLD) produced a statistically significant increase in PFS for OC-Pt patients [59]. This result was the outcome of the PRECEDENT trial; a randomized phase II study, that compared the combination of vintafolide + PLD with PLD alone [59]. Patients with FR positive cancer showed improved PFS compared to no PFS benefits in FR negative patients. After this successful phase II trial, a phase III trial called the PROCEED study was initiated (Study ID#: NCT01170650) to further evaluate the efficacy and safety of the vintafolide + PLD (Doxil) combination in OC-Pt patients. The main goal of the study is to determine PFS using version 1.1 of the response evaluation criteria in solid tumor (RECIST), and etarfolatide imaging to determine patients FR status [55]. Etarfolatide is a non-invasive, folate receptor-targeting companion imaging agent, which consists of a small molecule targeting the folate receptor and an imaging agent, which is based on technetium-99 m [55].

The targeting of the FR receptor appears to be promising strategy for OC-Pt cancer subsets that significantly overexpress these receptors. New folate conjugates are in development and this area of therapeutics is expected to consistently improve.

3.5. Insulin-like growth factor receptor inhibitors

The insulin-like growth factor (IGF) system consists of IGF-I, IGF-II, their target receptors (IGF-IR, IGF-IIR, insulin receptor (IR), and the insulin-related receptor (IRR)) as well as a family of six different IGF-binding proteins (IGFBPs) [60]. Upon binding of IGFs to IGF-1R and IR (but not IRR and IGF-2R), many signaling pathways can be activated. These downstream signaling mechanisms include the Ras-Raf-MAPK and PI3K-Akt transduction pathways. These transduction mechanisms result in stimulation of cell proliferation, motility, and inhibition of apoptosis [60]. All IGF-signaling system components are expressed in OC and likewise stimulate cell proliferation, invasive, and angiogenic activity of OC cells [61]. More

importantly, IGF-1R/IR inhibition in platinum-resistant ovarian cancer cells resensitizes them to the cytotoxic effects of cisplatin; indicating a role of the IGF system in OC-Pt [62]. This highlights a therapeutic opportunity for insulin and insulin-like growth factor receptor inhibition.

In the past few years, a number of inhibitors targeting the IGFR/IR have been developed, including antibodies against the receptors and small molecule receptor kinase inhibitors [63]. A trial (Study ID#: NCT01708161) with ganitumab (developed by Amgen), a human monoclonal antibody against IGF-IR, has been completed in patients with solid tumors including OC-Pts. This was a multi-center, open-label, phase Ib/II study. The aim of the phase Ib arm, was to estimate the median toxic doses and/or identify the recommended phase II dose(s) for the combination of BYL719 (a PI3K inhibitor) and ganitumab [64]. The phase II arm assessed the clinical efficacy and safety of the combination in OC patient populations including PIK3CA-mutated or -amplified OCs [64]. Data from this study are yet to be released, but will provide insight on the effect of ganitumab in OC-Pt.

A phase I/II trial (Study ID#: NCT00889382) with the small molecule, dual IGF-1R/IR tyrosine kinase inhibitor linsitinib (OSI-906) has also been completed [65]. The study evaluated intermittent and continuous linsitinib dosing and weekly paclitaxel in patients with recurrent EOCs including OC-Pts as well as other solid cancer types (endometrial and primary peritoneal) [65]. Of the 58 patients treated in the study, 3 OC patients showed a partial response, and stable disease was achieved in 10 OC patients. Pharmacokinetic studies showed no significant interactions when linsitinib was administered 2 h prior to paclitaxel. The most common drug-related toxicities were fatigue, nausea, hyperglycemia and drug eruption. Other details of the study outcomes related to PFS have not yet been published.

Many compounds are constantly being screened for IGF-IR inhibitory activity, but the similarity between the IGF-IR and the IR receptor presents a challenge for developing selective inhibitors for the IGF-IR. The main concern with this lack of selectivity is that dual inhibitors of IR and IGF-IR, has resulted in hyperglycemia in many clinical trials. This is a major hurdle to overcome in this area of OC therapeutics.

3.6. Epidermal growth factor receptor/human epidermal growth factor receptor family

The epidermal growth factor receptor (EGFR) is a member of the tyrosine kinase family of growth factor receptors. These receptors play a direct role in regulating cell proliferation, apoptosis, survival, cell differentiation, and migration [14]. The ERbB family of receptor tyrosine kinases includes EGFR (also known as HER1/ErbB1), EGFR2 (HER2/neu/ERbB2), HER3/ErbB3, and HER4/ErbB4 [66]. Dysregulation of the EGFR function has been linked to the pathology of OC [14] but evidence is conflicting; as other studies have not found strong evidence of a direct link between EGFR expression and function and OC progression. Many factors have been suggested for the mixed results; these include variability in

experimental methods, detection procedures, and scoring metrics. Despite the variable study outcomes in OC, evidence supports dysregulated EGFR ligand and receptor expression, heterologous regulation by GPCR ligands, and other non-ligand stimuli initiating chronic activation of EGFRs [14]. This chronic stimulation favors tumor development and progression [14].

The current therapeutic strategy is to inhibit EGFR activity using small molecule tyrosine kinase inhibitors or monoclonal antibodies [67]. Clinical trials have been conducted using the following agents alone and in combination: cetuximab, gefitinib, erlotinib, trastuzumab, and pertuzumab. These treatment regimens were evaluated in patients with recurrent or progressive disease, platinum-sensitive disease, and platinum-resistant/refractory disease among others [67].

Of note, the PENELOPE phase III trial investigated the efficacy of pertuzumab in combination with chemotherapy (single-agent topotecan, weekly paclitaxel, or gemcitabine) for treatment of platinum-resistant patients with downregulated human epidermal growth factor 3 (HER3) mRNA expression [68]. The results showed no significant improvement in PFS for the primary analysis (stratified hazard ratio, 0.74; 95% CI, 0.50–1.11; P = 0.14; median PFS, 4.3 months for pertuzumab plus chemotherapy versus 2.6 months for placebo plus chemotherapy). The study concluded that pertuzumab has the potential to be investigated further despite the lack of significance. To date, clinical trials evaluating anti-EGFR and HER therapies have shown minimal improvement in OC-Pt treatment outcome. Further studies evaluating inhibitors of downstream signaling and simultaneous antagonism of the EGFR and HER have been recommended [66].

4. Immunotherapy and advances in immunotherapeutic combination strategies in ovarian cancer

Current chemotherapeutic regimens for OC-Pt patients whether monotherapy or combinatorial are inadequate. Immunotherapeutic approaches are now being increasingly explored for these patients where a therapeutic ceiling has been reached with standard chemotherapy. Immunotherapy in OC-Pt patients is just emerging and is currently restricted to clinical trials that have shown promising results. The American Cancer Society defines cancer immunotherapy as ‘treatment that uses your body's own immune system to help fight cancer’. Within the tumor microenvironment, the pathological interactions between cancer cells and immune cells is complex and most events spiral into an immunosuppression that causes tumor cells to proliferate and evade immune system attack [69]. There are several categories of immunotherapeutic agents that either stimulate the body’s immune system’s ability to eradicate cancer cells (e.g. cancer vaccines and adoptive T cell transfer), target proteins on the surface of T cells that prevent them from attacking cancer cells (e.g. immune checkpoint inhibitors), or identify specific abnormalities on the surface of cancer cells that render them susceptible to targeted agents (e.g. monoclonal antibodies) [69]. Many of these drugs are being evaluated in OC-Pt patients and are discussed below.

4.1. Immune checkpoint inhibitors

Checkpoint proteins are molecules found on the surface of T cells that prevent them from attacking cancer cells [70]. Two such proteins are cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1) [71]. PD-1 is expressed on the surface of activated T cells and its ligands, PD-L1 and PD-L2 are found on the surface of dendritic cells or macrophages [70]. Interaction of PD-1 with either PD-L1 or PD-L2 results in inhibition of T cell signaling, reduction in T cell numbers, and increased susceptibility of T cells to apoptosis [71]. CTLA-4 regulates T cell priming and activation in the initiation phase of the immune response [71]. The high expression of PD-L1 and PD-L2 on OC cells is associated with shorter PFS [72]. Similarly, evidence suggests that OC patients with low CTLA-4-mediated signals have a better prognosis than patients with high CTLA-4 activity [73].

4.1.1. Anti-PD-1/PD-L1 antibodies

Several antibodies directed against PD-1 (pembrolizumab, nivolumab, and avelumab), PD-L1 (atezolizumab and durvalumab), and CTLA-4 (ipilimumab) have been evaluated in OC. Nivolumab (Opdivo) is a fully humanized IgG4 antibody that blocks the engagement of PD-1-by-PD-1 ligands [74]. Nivolumab was administered every 2 weeks to patients with advanced or relapsed OC-Pt and response rate was assessed by RECIST [74]. The study included 15 OC-Pt patients and the drug showed encouraging clinical efficacy. Some adverse drug reactions including fever, disorientation, and gait disturbance were observed. A dose escalation study (Study ID#: UMIN000005714) is now under way as a second arm of this trial.

Avelumab (Bavencio) is a fully human monoclonal antibody of isotype IgG1 that targets PD-L1. It was evaluated in a phase Ib (Study ID#: NCT01772004) expansion study in 75 patients with recurrent/refractory OC which included OC-Pt [75]. Of this cohort, 8 patients showed a partial response and 33 patients displayed stable disease, which was reported as a disease control rate of 54.7%.

One other phase Ib study (KEYNOTE-028/Study ID#: NCT02054806) evaluated the anti-tumor activity and safety of pembrolizumab (Keytruda) in patients with PD-L1 positive advanced OC which included patients refractory to platinum therapy [76]. Pembrolizumab is a humanized antibody that binds to and blocks PD-1. PD-1 blockade with pembrolizumab was well tolerated and displayed anti-tumor activity. Of the 26 patients enrolled in the study, 1 achieved complete response, 2 partial response, and 6 had stable disease. The most common adverse events were fatigue (42.3%), anemia (30.8%), and decreased appetite (30.8%).

The role of the PD-1/PD-L1 axis is continuously been studied and characterized in OC and with new information on OC-Pt immunogenicity emerging consistently, this disease is expected to remain a focused target of PD-1/PD-L1 based therapeutics.

4.1.2. Anti-CTLA4 antibodies

Inhibition of CTLA-4 during the T cell priming/activation step leads to dysregulated expansion of auto-reactive T cells, including tumor-specific T cells [73]. The anti-CTLA 4 monoclonal antibody ipilimumab (Yervoy) has shown anti-tumor effect in stage IV OC. Ipilimumab is a recombinant human monoclonal antibody (IgG1 kappa immunoglobin) that antagonizes the CTLA-4 immune checkpoint. The administration of ipilimumab to 11 stage IV OC patients previously vaccinated with granulocyte-macrophage colony-stimulating factor (GM-CSF)-modified irradiated autologous tumor cells showed promising results [77]. Ipilimumab caused a reduction or stabilization of CA-125 levels in these patients and no serious toxicities directly attributable to the antibody were observed.

Tremelimumab is a fully human IgG2 monoclonal antibody to CTLA-4. The combination of tremelimumab with the immunotherapeutic agent durvalumab is currently undergoing a phase I trial (Study ID#: NCT01975831) which includes OC-Pt patients [78]. The primary endpoints of this study are to evaluate safety and identify the maximum tolerated dose of the combination. The secondary objectives are to determine effects on tumor response and PFS. Preliminary data show that the combination has a manageable safety profile, with evidence of clinical activity. Trials with anti-CTLA-4 inhibitors in other cancer types have been associated with significant immune-related toxicities [79], and this might be the major limitation in terms of advancing their application in OC-Pt. More clinical trials are needed in this area of OC-Pt therapeutics.

4.2. Cancer vaccines

The aim of vaccinations in cancer patients is to sensitize the immune system to recognize, target, and eradicate tumor cells in an approach that employs both adaptive and innate immunity [80]. Vaccines aim to provoke a tumor-specific immune response by increasing tumor-associated antigen (TAA) presentation by antigen-presenting cells (APCs) which subsequently generates tumor-antigen specific cytotoxic T lymphocytes [80].

Dendritic cell, peptide, and recombinant viral vaccines are the main types currently undergoing clinical trials for OC. One promising TAA for dendritic cell vaccines is mucin 1 (MUC-1). MUC-1 is a heavily glycosylated, type 1 transmembrane protein that is overexpressed in a large number of cancers including OCs [81]. While multiple MUC-1 vaccines are now in development, CVac (developed by Prima BioMed) is the leading candidate for OC. In the CAN-003 phase II study, 63 confirmed Stage III or IV OC patients received CVac [82]. While the study cohort did not disclose if the patient cohort included OC-Pts, CVac demonstrated positive trends in progression free survival and immune responses and further studies in OC-Pt patients are warranted.

A dendritic cell vaccine pulsed with autologous hypochlorous acid-oxidized OC lysate was also evaluated in a pilot study (Study ID#: NCT01132014) of five subjects with recurrent OC [83]. Of the five patients who received the DC vaccine, two had PFS of 24 months or more.

Peptide vaccines rely primarily on the immunogenicity of the injected peptides to stimulate an immune response. In the cancer setting, the peptides chosen for the vaccine are TAAs.

A phase I trial of the NY-ESO-1 OLP vaccine showed promising results in advanced OC patients that initially received chemotherapy with at least one platinum-based chemotherapy regimen [84]. NY-ESO-1 OLP contains synthetic overlapping long peptides (OLP) from the cancer-testis antigen NY-ESO-1 [84]. The vaccine was found to be safe and rapidly induced consistent integrated immune responses in nearly all vaccinated patients. A phase I/IIb multicenter study was also conducted to evaluate the safety and immunogenicity of the anti-idiotypic antibody vaccine ACA125 in 119 patients with advanced ovarian carcinoma (including OC-Pt patients) [85]. ACA125 functionally imitates the tumor antigen CA125. Preliminary evidence demonstrated safety and immunogenicity of the vaccine. The study data has not reveal conclusions regarding OC-Pt subgroups and this requires further evaluation.

Recombinant viral vaccines utilize genetically modified viruses as vectors for introducing TAA-encoding DNA into cells within the body. PANVAC is a vaccine with payload delivered through two viral vectors: recombinant vaccinia and recombinant fowlpox [86]. The vectors contain transgenes for the tumor-associated antigens epithelial mucin 1 (MUC-1) and carcinoembryonic antigen (CEA). Overexpression of MUC-1 and CEA is seen in OC [87, 88]. In a pilot study of PANVAC in 14 OC patients (including OC-Pt), median time to progression was 2 months and median OS was 15.0 months [86].

4.3. Adoptive cell therapy

Adoptive cell therapy (ACT) involves the infusion of tumor antigen cells to stimulate innate anti-tumor immunity and induce cancer regression [89]. A pilot study in which seven patients with recurrent local OC were given multiple cycles of intraperitoneal infusions of autologous MUC1 peptide-stimulated cytotoxic T lymphocytes has been completed [90]. Clinical benefit was seen in only one patient who was disease free >12 years. While it is difficult to interpret this information in the context of OC-Pt, the study is worth mentioning as at least one patient had received prior platinum therapy.

A phase I clinical trial of adoptive transfer of folate receptor-alpha-redirected autologous T cells for recurrent OC cancer was initiated to establish the safety and proof of concept of autologous FRα-redirected T cells administered intravenously, in subjects with recurrent stage II to IV FRα-positive epithelial ovarian carcinoma (including OC-Pt subgroups) [91]. It is also possible that ACT can be used in combination strategies but the challenge with solid tumors such as OCs; is that tumor microenvironment immunity can cause immunosuppression and render ACT ineffective.

4.4. Toll-like receptors agonists (TLRs)

Toll-like receptors (TLRs) comprise a family of 13 receptors found on hematopoietic and non-hematopoietic cells [92]. The TLR8 subtype is mainly found in monocytes and dendritic cells

and it plays an important role in the immune response by recognizing single-stranded RNAs as its natural ligand. Motolimod (Motolid/formerly known as VTX2337) is a synthetic, small molecule, selective agonist of TLR8 that stimulates natural killer cell activity and enhances antibody-dependent cellular cytotoxicity [92]. A phase II randomized, double-blind, placebo-controlled study (Study ID#: NCT01294293), evaluated chemo-immunotherapy combination using motolimod with PLD in recurrent or persistent OC [92]. While the addition of motolimod to PLD did not significantly improve overall survival or PFS, the combination was well tolerated, with no synergistic or unexpected serious toxicity. Another phase II study is also now underway (Study ID#: NCT01666444) in patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The purpose of this study is to compare the overall survival of patients treated with motolimod + PLD versus those treated with PLD alone in women with recurrent or persistent, epithelial ovarian, fallopian tube, or primary peritoneal cancer. This study will provide further insight on the future of motolimod in OC-Pt.

5. Combination strategies with immunotherapy

Over the past decade we have learned that OC in general responds poorly (11–25% overall) to single-agent immunotherapy; especially checkpoint blocking strategies [93]. There is very limited data regarding response rates of OC-Pt subgroups specifically, but in most cases these cohorts of patients are integrated in general OC study data, suggesting similar patterns of response. When reviewed collectively, the data suggest that efficient anti-tumor immune response is likely to require combinatorial therapeutic strategies that simultaneously target different stages of tumor escape. Combinations involving immune checkpoint inhibitors, anti-angiogenic agents, and PARP inhibitors are gaining momentum in clinical OC-Pt research and are highlighted below.

5.1. Checkpoint inhibitor + PARP inhibitor

Currently, several trials combining PARP and immune checkpoint inhibitors are ongoing [94]. An open-label dose escalation study (Study ID#: NCT02485990) of tremelimumab alone or combined with olaparib for recurrent or persistent OC is currently recruiting participants. This study is aimed at determining what dose of tremelimumab and olaparib is safe and effective in patients with persistent OC including those with OC-Pt.

A phase I/II Study (Study ID#: NCT02484404) of durvalumab in combination with olaparib and/or cediranib for advanced solid tumors including OC-Pt is currently recruiting. The aim of the phase I arm is to determine the safety of the combination of durvalumab with olaparib or cediranib. Phase II studies will determine the efficacy of these combination in treating OC.

The TOPACIO trial (Study ID#: NCT02657889) will evaluate niraparib in combination with pembrolizumab in patients with triple-negative breast cancer or OC-Pt. The primary

outcome measures are to determine dose-limiting toxicities of combination treatment with niraparib and pembrolizumab and to determine the objective response rate using RECISTv1.1.

5.2. PARP inhibitor + anti-angiogenic agent

The OCTOVA study (Study ID#: NCT03117933), is currently recruiting participants for a randomized phase II trial investigating the efficacy of chemotherapy plus olaparib and cediranib combination therapy in patients with BRCA-mutated OC-Pt. Patients will be randomized to one of three treatment groups: olaparib only, olaparib and cediranib, and the control group paclitaxel. The aim is to compare efficacy and tolerability of the three treatments.

5.3. Checkpoint inhibitor + anti-angiogenic agent

A phase II study (Study ID#: NCT02659384) to evaluate the combination of atezolizumab plus bevacizumab and acetylsalicylic acid in recurrent OC-Pt is currently recruiting. The primary aim is to determine PFS at 6 months by RECIST.

5.4. Checkpoint inhibitors + cancer vaccine

The administration of ipilimumab in 11 patients with metastatic ovarian carcinoma after vaccination with irradiated autologous tumor cells engineered to secrete GM-CSF (GVAX), showed promising results [95]. Three patients achieved stable disease as measured by CA-125 levels, and one patient achieved an objective response by radiographic criteria and maintained disease control over 4 years with regular infusions of anti-CTLA-4 antibody.

6. Challenges and future perspectives

There are still many hurdles to overcome in the treatment of OC-Pt but some progress has been made in recent years, especially with the development of new immunotherapeutic agents. The good news is that OC cancer is a targetable tumor and although the OC-Pt subgroup of patients have biologically distinct tumors, both targeted therapies and immunotherapy offer an opportunity to uniquely address these differences. As new agents are developed in these categories, the main challenge with existing and future clinical trials will be the risk of adverse events and toxicities, especially with combination immunotherapeutic regimens, where there is an elevated risk for adverse immune events. A second challenge is the optimization of the dose and schedule of immunotherapeutic combinations in order to maximize the overall risk-benefit profile of a given combination. This requires multiple clinical trials with dose escalation studies that can be expensive. This approach is necessary however, especially in the setting of platinum-resistant OC cancer where much research is still needed.

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